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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,163	12/20/2001	Sanjay Lakhota	AM100039	1674
25291	7550	04/07/2008		
WYETH PATENT LAW GROUP 5 GIRALDA FARMS MADISON, NJ 07940			EXAMINER FORD, VANESSA L	
			ART UNIT	PAPER NUMBER
			1645	
			MAIL DATE	DELIVERY MODE
			04/07/2008 PAPER	

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

**Application No.**

10/019,163

**Applicant(s)**

LAKHOTIA ET AL.

**Examiner**

VANESSA L. FORD

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 11 October 2007.  
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.  
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-16 is/are pending in the application.  
4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.  
6) ☒ Claim(s) 1-16 is/are rejected.  
7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.  
8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.  
10) ☒ The drawing(s) filed on 20 December 2007 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☒ All b) ☐ Some \* c) ☐ None of:  
1. ☒ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)  
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)  
3) ☐ Information Disclosure Statement(s) (PTO/5508)  
Paper No(s)/Mail Date \_\_\_\_\_  
4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_  
5) ☐ Notice of Informal Patent Application  
6) ☐ Other: \_\_\_\_\_

**DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment filed October 11, 2007 has been entered. Claim 6 has been amended. Claims 1-16 are under examination.

***Rejection Maintained***

2. The rejection under 35 U.S.C. 103(a) is maintained for claims 1-16 for the reasons set forth on pages 3-4 paragraph 4 of the previous Office Action.

The rejection is reiterated below:

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. The rejection under 35 U.S.C. 103(a) is maintained for claims 1-16 for the reasons set forth on pages 2-5 paragraph 4 of the Final Office Action.

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The rejection was on the grounds that Green et al teach a method of purifying bacteria using detergents such as Triton™ (column 4). Green et al teach that in a preferred embodiment the outer membrane components are prepared by differential solubilization of the inner membranes and outer membranes using Triton™ in HEPES-NaOH and MgCl<sub>2</sub> (Abstract and column 14). Green et al teach that a subfraction of the preparation of the outer membrane components which is rich in protein "e" (outer membrane protein P4 from *Haemphilus influenzae*) can be produced by extraction with an aqueous solution (column 4). Green et al teach that the protein "e" from the outer membrane cell wall complex can be then achieved by a two-step differential solubilization with sulfobetaine detergents (column 4). Green et al teach that the first step comprises an aqueous solution of Zwittergent™ to remove other outer membrane proteins other than protein "e" (column 4). Green et al teach that the residual insoluble components are then extracted with an aqueous solution of Zwittergent™ and this fraction results in the solubilization of protein "e"(column 4). Green et al teach that this process is performed in a homogenizer (column 14) since the instant specification teaches that a homogenizer is a microfluidizer (page 10 of the specification). Green et al teach that recombinant protein "e" can be isolated and purified by differential solubility (column 9).

Green et al do not teach tangential flow filtration (TFF).

Nicholson teaches a method of extracting recombinant proteins using tangential flow filtration (TFF) (column 10). Nicholson et al teaches that using their method is advantages because the proteins purified by the method have a high yield and was entirely homodimeric (see the Abstract).

It would be *prima facie* obvious at the time the invention was made to use tangential flow filtration as taught by Nicholson to extract bacterial proteins (inner and outer membrane) because Nicholson teaches that using TFF has the benefit of high yields and entirely homodimeric. It would be expected barring evidence to the contrary that using tangential flow filtration in a method of extracting proteins would offer high quality and high yield proteins.

#### Applicant's Arguments

Applicant urges that in everyone of the pending claims the claimed process of extracting proteins begins with lysis of the bacterial cells containing the proteins in a fermentation broth. Applicant urges that they respectfully disagree. Applicant urges that to establish a case of *prima facie* obviousness all claim limitations must be taught or suggested by the prior art.

Applicant urges regarding motivation to combine the prior art references that the Supreme Court warned that caution must be considered regarding hindsight reasoning. Applicant urges that the Examiner has failed to provide adequate articulated reasoning with some rational underpinning to support a legal conclusion of obviousness. Applicant urges that there is no motivation to combine the teachings of Green et al and Nicholson et al. Applicant urges that all of the claims comprising lysing the bacteria or bacteria host cells in fermentation broth followed by diafiltration of the lysed fermentation broth. Applicant urges that Green et al teach that the lysing step is performed using a homogenizer but provides no explanation as to the lysing step occurs. Applicant urges according to Green et al, cells are first isolates and removed from the fermentation broth by centrifugation, pelleting and resuspension in HEPES buffer. Applicant urges it is not until after resuspension that the cells are lysed.

Applicant urge irrespective of the inclusion of tangential flow filtration, Green et al and Nicholson et al do not describe the presently claimed process comprising lysing bacteria or bacterial host cells in a fermentation broth followed by diafiltration of the lysed fermentation broth.

#### Examiner's Response to Applicant's Amendments

Applicant arguments filed October 11, 2008 have been fully considered but they are not persuasive.

It is the Examiner's position that Applicant is arguing the references individually. It should be remembered that it is the combination of references that teaches the claimed invention.

In response to applicant's argument that there is no motivation to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the skilled artisan would be motivated to use tangential flow filtration as taught by Nicholson in the method of extracting proteins of Green et al because Nicholson tangential flow filtration (TFF) removes low molecular weight compounds. Nicholson et al teaches that using their method has advantages because the proteins purified by the method have a high yield and was entirely homodimeric. Therefore, one of ordinary skill in the art would be motivated to use TFF in extraction methods to arrive at purified products.

The Examiner disagrees with Applicant's assertion that the combination of references do not teach lysing bacteria or bacterial host cells in a fermentation broth followed by diafiltration of the lysed fermentation broth. It should be noted that Green et al teach that an alternative source culture medium (fermentation broth) of *H. influenza* cells (bacteria cells) can be used (column 4, paragraph 4). As stated above, it is the combination of references that teach the claimed invention.

It should be noted that Nicholson is used to teach that *after cells have been* lysed, tangential flow filtration is used to remove low molecular weight components.

Therefore, one of ordinary skill in the art would be motivated to use TFF in extraction methods to arrive at purified products. One of ordinary skilled in the art would have a reasonable expectation of success by combining the prior art references to arrive at the claimed invention.

In view of all of the above, there is nothing on the record to suggest that the combination of reference does not teach the claimed invention.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". Thus, it would be obvious to

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apply a known technique to be used in a known method that is ready for improvement to yield predictable results such as high quality and high yield proteins.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that it is obvious to combine prior art elements according to known method to yield predictable results. Thus, the combination of prior art references as combined provided a *prima facie* case of obviousness absent evidence to the contrary.



***Status of Claims***

4. No claims allowed.

***Conclusion***

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/  
Examiner, Art Unit 1645  
Biotechnology Patent Examiner  
March 31, 2008

/Shanon A. Foley/  
Supervisory Patent Examiner, Art Unit 1645